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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/912,697	07/25/2001	Nicholas C. Nicolaides	MOR-0040	5193

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EXAMINER	
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ART UNIT	PAPER NUMBER
1648	

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8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/912,697	NICOLAIDES ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *4-13, 28-37, and 39-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,14-27 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 1-41 are pending in the application. Claims 1-3, 14-27, and 38 are under consideration to the extent that they read on the elected invention. Claims 4-13, 28-37, and 39-41 are withdrawn from consideration.

Election/Restrictions

2. Applicant's election with traverse of Group I, and subgroup (A3) and (i) in Paper No. 7 is acknowledged. The traversal is on the ground(s) that Groups (A1)-(A3), and (A)-(C) should be examined together as they methods of Groups (A1)-(A3) are similar, and the methods of (A)-(C) are the same, and that it would be not be unduly burdensome to examine all the inventions together, especially as they are not classified in different classes of inventions. These arguments are not found persuasive. Each of the inventions of Groups A1-A3 involve the use of different compounds to block mismatch repair. Thus, each of these methods requires a different search not coextensive with the search required for the other embodiments. Further, these different methods may perform the same function, albeit through different modes of operation, but they are not disclosed as usable together. This is because no one of these methods is involved in the processes being carried out by another of the methods.

The applicant also traversed the restriction between Groups A-C for substantially the same reasons. Again, each of these methods requires a different search because they each use a

different process for the induction of mismatch repair in the bacterium. As each of these processes involved steps and methods not used by the others, a separate search is required for these different processes.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 4-13, 28, 29, 35-37 and 39-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7

4. Claims 30-34 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7. Although traversal was made of the restriction among the subgroups OG Group I, the applicant did not present any grounds of traversal between Groups I and II. Further, by indicating that he applicant traversed the restriction only "in part" (page 2, paper 7), and by present arguments against the other restriction requirements, the applicant has indicated that they did not traverse this requirement.

5. For the applicant's convenience, it should be noted that a matrix type restriction is merely a format for setting out the restriction groups. After the first election, no further election is required by the applicant. If other groups are rejoined under the linking claim practice, this is because the linking claim itself has been found to be allowable. In such a case, further restriction would be inappropriate.

Information Disclosure Statement

6. The reference WO 98/48041 (of record in the IDS filed on February 4, 2002) is in a foreign language accompanied by an English abstract. Due to this, the reference has been examined only to the extent of the disclosure in the abstract.

7. The Sambrook references identified as references DS and DT in the information disclosure statement filed December 31, 2001, are not in compliance with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The applicant has not provided a copy of the references to the Examiner. Further, the applicant explains that the references were "too voluminous" to be sent to the Examiner. If the applicant desires such voluminous references to be considered, they should provide, as required by 37 CFR 1.98(a)(2) a reference or copy of "that portion which caused it to be listed." As the applicant has not complied with the requirements of 37 CFR 1.98, these references have not been considered.

Claim Objections

8. Claim 26 is objected to because of the following informalities: the word "multiantiboitic" is a misspelling of the word "multiantibiotic." Appropriate correction is required.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1-3, 15, and 38 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Pre-Grant Publication 2002/0068284 issued to Nicolaides et al. (Nicolaides 1). These claims read on methods of generating antibiotic resistant bacteria by blocking mismatch repair in the bacterium by introducing a dominant negative allele of the PMS2-134 mismatch repair gene into the bacterium, contacting the bacterium with at least one antibiotic, selecting bacterium resistant to that antibiotic and culturing the bacterium. Claim 15 further specifies that the antibiotic against which resistance is generated is an aminoglycoside. Claim 38 describes an antibiotic resistant bacterium generated by the method of claim 1.

Nicolaides 1 teaches such a method in Example 2 of the publication. Page 7. In the disclosed method, the reference creates a bacterium expressing PMS134, a dominant negative allele of a human mismatch repair gene. Page 5-6, paragraph 0045, and page7, paragraphs 0054-0055. The PMS134 (residues 1-134 of SEQ ID NO: 22 in the reference) gene appears to be identical to the PMS2-134 gene (SEQ ID NO: 14 in the present application). The disclosed method teaches the generation of Kanamycin resistant bacterium. Kanamycin is a aminoglycoside antibiotic. Thus, the reference anticipates the claimed invention.

11. Claim 38 is rejected under 35 U.S.C. 102(b) as being anticipated by the teachings of either of Johnston et al, U.S. patent 6,043,048 or Lin, U.S. Patent 6,025,400. The rejected claim reads on any bacterium with antibiotic resistance that may be produced by the method of claim 1. In the U.S., the patentability of a claim to product derived through a specified process is determined by the patentability of the product itself. See, MPEP §2113; and In re Thorpe, 227 U.S.P.Q. 964, at 966 (Fed. Cir. 1985). Thus, the rejected claim is anticipated by any bacterium with antibiotic resistance that may be made by the claimed method.

Each of the Johnston and Lin references indicate that bacterium with antibiotic resistance were known in the art prior to the applicant's invention. Further, the present invention is not limited to any bacterium with a particular mutation that makes it resistant to an antibiotic. The claimed method is capable of producing any bacterium with antibiotic resistance, including those already known in the art. Thus, the claim to an antibiotic resistant bacterium is anticipated by the prior art as demonstrated by the disclosed references.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-3, 15, 27, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolaides 1 as applied against claims 1-3 above. The Claim 27 describes the method of claim 1, further comprising a step of making the antibiotic resistant bacteria genetically stable. In the specification, this step is described as making a transgenic construct that restores mismatch repair to the bacterium after trait selection. Pages 16-17. Nicolaides 1 also teaches this step. Page 5, paragraphs 0043-0044. Although the reference does not teach the stabilization step with reference to the Kanamycin resistant bacteria described above, it would have been obvious to one skilled in the art to make such a stable bacteria from the teachings of the reference.

14. Claims 1, 19, 27, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iris et al., U.S. Patent 6,221,585, in view of Stemmer et al., U.S. PG Pub. 2002/0049104, and Johnston et al., U.S. Patent 6,043,048. Claim 1 describes a method of generating antibiotic resistant bacteria by blocking mismatch repair in a bacterium, contacting the bacterium with at least one antibiotic, and selecting and culturing the antibiotic resistant bacterium. Claim 27 adds a further step of genetically stabilizing the antibiotic resistant bacterium generated. Claim 38 describes a bacterium generated by these methods.

Iris teaches a method of identifying genes in microbes or other cells that confer on that cell a certain phenotype. Abstract, column 8, lines 11-32. Among the phenotypes for which the method is identified as useful in identifying is susceptibility or resistance to antibiotics. Column 9, lines 26-31. One of the methods described by Iris involves the isolation of genetic variants of a cell population that have the phenotype of interest. Col. 19, lines 2-34. This reference also teaches that identification of such genes is useful in the development of strategies for disease

control. Abstract, columns 1-2. Thus, this reference teaches that is beneficial to screen for cells expressing a particular phenotype, including antibiotic resistance in bacterium, such that the genes responsible for these phenotypes may be isolated and used to develop disease treatments. However, while this reference also mentions mismatch repair (columns 7-8), the methods described focus on the comparison of genes expressed among cells of different phenotypes.

Stemmer also teaches methods of identifying the genes that control specific phenotypes. Abstract, page 1, paragraph 0003. Stemmer also indicates that a useful feature in such screening is the generation of diversity in the cells being examined. Page 11, paragraph 0114. Among the techniques disclosed for generating such diversity is the use of mutagenesis using repair deficient host strains. Page 12, paragraph 0119. Thus, this reference suggests to those in the art that, in a method to isolate cells of a particular phenotype, it is useful to generate diversity in among the cell populations being studied.

When viewed together, it would be obvious to a person of ordinary skill in the art to use mismatch deficient cells in the method of Iris to stimulate diversity in the populations of cells being examined for the phenotype of interest. Further, as demonstrated by the Johnston reference (column 2, lines 56-65), it is known in the art that antibiotic resistant bacterium may be identified by contacting and culturing bacterium in the presence of the antibiotic against which resistance is sought. Such a method comprises all of the steps of contacting the bacterium with the antibiotic, selecting the bacterium (non-resistant bacterium are killed), and culturing the bacterium. Thus, it would have been obvious to one of ordinary skill in the art to have combined these references to such that the bacterium being cultured in the presence of the antibiotic would be mismatch repair deficient (i.e. mismatch repair is blocked). This would increase the phenotypic diversity of the

bacterial cells, and lead to greater diversity both between the cells that are not resistant compared to those that are, but also among the cells that are resistant.

The motivation for this is two-fold. First, one of ordinary skill in the art would have been motivated by Stemmer to use the method of diversity generation to increase the likelihood that the mutations leading to the desired phenotype would occur. Further, another reference, Ashby et al., U.S. Patent 6,518,035, provides a motivation for desiring a multiplicity of phenotypes leading to antibiotic resistance. The reference teaches that approaches in the art for developing drugs targeting antibiotic resistance mechanisms in bacterium suffers because such development often targets the same bacterial processes. Column 2, lines 17-26. It would thus be obvious to one of ordinary skill in the art that one way of potentially avoiding this problem would be to generate multiple phenotypes that are resistant to the antibiotic, and thereby increase the chances that one or more of these phenotypes are resistant due to bacterial processes not previously encountered. Thus, one of ordinary skill in the art would have been motivated to combine these references to develop the disclosed method of antibiotic resistant bacterium. As the method of generating the bacterium is obvious, the bacteria so generated are also obvious.

Although none of these references teach the additional step of genetically stabilizing the generated bacterium, such a step would have been obvious to one of ordinary skill in the art. The purpose of such a method is to generate resistant bacterium such that the reason for its resistance can be determined, and if it has not been previously encountered, so that a drug against the new strain may be developed. These post-generation processes would not be very useful in the absence of the ability to stabilize the new strains such that they may be studied in a stable form.

One of ordinary skill in the art would have had a reasonable expectation of success in the combination as none of the steps joined in the combined method were new to the art, and because no one step would be likely to interfere with the other steps.

15. Claims 1, 2, 19, 27, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iris in view of Stemmer and Johnston as applied to claims 1, 27, and 38 above, and further in view of Aronshtam and Marinus, Nucleic Acids Research, 24(13):2498-2504. Claims 1 and 38 have been described above. Claim 2 describes the method of claim1 wherein bacterial mismatch repair is blocked by introducing a dominant negative allele of a mismatch repair gene into the bacterium. The teachings of the Iris, Stemmer, and Johnston references have also been described above. None of these reference either teach or suggest the inclusion of a dominant negative allele in the bacterial genome to block mismatch repair in the cell.

Aronshtam does teach such a method of inhibiting mismatch repair. The reference teaches several dominant negative mutations to the mutL gene of E. coli that lead to increased mutagenesis. See, abstract, pages 2501-2502. The reference also teaches that these mutations lead to an increase in the number of antibiotic resistant mutations that arise in bacterial cultures. See, page 2501, right column; and Table 3, page 2502. Thus, it would have been obvious to one skilled in the art desiring to generate multiple antibiotic resistant bacterium to increase the number of phenotype diversity as suggested by Stemmer by inserting the dominant negative alleles taught by Aronshtam into the bacterial cells. Such a person would have had a reasonable expectation of success given the teachings of Aronshtam showing that inclusion of these alleles generally lead to higher number of mutations leading to antibiotic resistance.

16. Claims 1, 2, 19, 27, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston in view of Iris and the combined teachings of LeClerc and either Drummond or Moreland. The rejected claims have been described above. Johnston has also been described above as describing the identification of antibiotic resistant bacterium may be identified by contacting and culturing bacterium in the presence of the antibiotic against which resistance is sought. Such a method comprises all of the steps of contacting the bacterium with the antibiotic, selecting the bacterium (non-resistant bacterium are killed), and culturing the bacterium. Although the method taught by Johnston describes the generation of a beta-lactam resistant bacterium, the same method is generally applicable for all antibiotics. However, Johnston does not teach either a motivation for the generation of new antibiotic resistant bacterium, or a step of inhibiting mismatch repair in the bacterium to induce mutagenesis leading to generation of such resistance.

Iris teaches that the identification of genes responsible for a given phenotype would be useful in the identification of new drugs and therapies. Abstract. Among the phenotypes suggested as beneficial targets is the resistance of microbes to antibiotics. Col. 9, lines 26-27. Thus, the Iris reference provides a motivation for the generation of new forms of antibiotic resistant bacteria. However, Iris still does not teach the step of blocking mismatch repair in order to induce the formation of such bacteria variants.

LeClerc teaches that a defect in the mismatch repair of Esherichia coli and Salmonella enterica lead to increased emergence of antibiotic resistance in the bacterial cells. Further, each of the Drummond and the Moreland references teach that drug resistant cells were generated by

introducing mismatch repair defects into them (thereby blocking mismatch repair). Thus, these references suggest to those of ordinary in the art that in order to generate a number of drug resistant bacterium quickly, they could introduce such a defect into the target strain. It would then have been obvious to such a person to use the mismatch repair defective bacterium in the screening assay described in Johnston to generate and identify the bacterium. Since the identified references render the claimed method obvious, the likewise render the bacteria generated using the method obvious.

Although none of these references teach the additional step of genetically stabilizing the generated bacterium, such a step would have been obvious to one of ordinary skill in the art. The purpose of such a method is to generate resistant bacterium such that the reason for its resistance can be determined, and if it has not been previously encountered, so that a drug against the new strain may be developed. These post-generation processes would not be very useful in the absence of the ability to stabilize the new strains such that they may be studied in a stable form.

17. Claims 1-3, and 27, 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iris in view of Stemmer and Johnston as applied to claims 1,2, 27, and 38 above, and further in view of either Nicolaides et al., Molecular and Cellular Biology, 18(3):1635-1641 (Nicolaides 2) or Nicolaides et al., U.S. Patent 6,146,894 (Nicolaides 3). Claims 1, 2, and 38 have been described above. Claim 3 limits the claimed invention to embodiments wherein the mismatch repair is blocked by introducing the PMS2-134 dominant negative allele of a mismatch repair gene into a bacterium. The teachings of the Iris, Stemmer, and Johnston references have also

been described above. None of these reference either teach or suggest the inclusion of a dominant negative allele in the bacterial genome to block mismatch repair in the cell.

However, while the previously described references do not describe such a method, both Nicolaides 2 and Nicolaides 3 either teach or suggest that an organism, including bacterial cells, may be made hypermutable by insertion of a dominant negative allele of a mismatch repair gene. Nicolaides 2, title, abstract, and pp. 1640-41; and Nicolaides 3, abstract. In particular, each of these references teach that one such dominant negative allele that may be used comprises a gene coding for the first 134 residues of protein encoded by the hPMS2 gene (referred to in here and in claim 3 as the PMS2-134 gene). Nicolaides 2, p. 1635, right column; and Nicolaides 3, column 4, lines 8-12. In view of these teachings, it would have been obvious to one of ordinary skill in the art to have made the repair deficient bacterium as suggested by Stemmer by inserting into the bacterium the dominant negative alleles as taught by either Nicolaides 2 or Nicolaides 3.

The motivation for one of ordinary skill in the art to make this combination would be that the method is a known method of inducing a mismatch repair deficiency. There would have been a reasonable expectation of success due to the teachings of either of the Nicolaides references suggesting or stating the insertion could inactivate mismatch repairs in other cells (Nicolaides 2, pp. 1640-41; Nicolaides 3, columns 3-4), including in bacteria (Nicolaides 3, column 4, lines 23-25). These teachings are supported by the teaching of Nicolaides 2 that show that a human dominant negative allele caused hypermutability in a hamster, and by the teachings of Harfe et al. (Annu. Rev. Genet. 34:359-99), indicating that the mismatch repair proteins for bacteria and mammals are highly conserved. In view of these teachings, and the teachings of Nicolaides 3, one of ordinary skill in the art would have had a reasonable expectation that the dominant

negative allele taught by Nicolaides 2 would be effective in generating hypermutability in bacterium.

18. Claims 1, 14-26, 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Iris in view of Stemmer and Johnston as applied to claims 1, 19, and 38 above, or over Johnston in view of Iris and the combined teachings of LeClerc and either Drummond or Moreland as applied to claims 1, 19, and 38 above, further in view of Lin (U.S. Patent 6,025,400, column 1), Chang et al. (U.S. Patent 6,043,220, column 1), Setterstrom et al. (U.S. Patent 6,410,056, column 4), and The Merck Index, (1983, pages 2036, 5032-33,and 6448-449). Claims 1 and 38 have been described above. Claims 14-25 each describe the method of claim 1 wherein the antibiotic against which resistance is sought is a known antibiotic described in the claims respectively as a quinilone, an aminoglycoside, a magainin, a defensin, and tetracycline, a beta-lactam, a macrolide, a lincosamide, a sulfonamide, a chloramphenicol, a nitrofurantoin, or an isoniazid. The Iris, Stemmer, Johnston, LeClerc, Drummond, and Moreland references have been described above. Lin was also described in part above.

The remaining references identify the claimed groups of antibiotics as antibiotics or antimicrobials known in the art. As these antibacterial drugs were known in the art, it would have been obvious to one of ordinary skill in the art to generate bacteria resistant to any one of these compounds.

Claim 26 specifies that the method of claim 1 is used to generate bacteria resistant to multiple antibiotics. Although the references identified above do not specifically disclose that the methods may be used to identify bacteria with multiantibiotic resistance, such would still have

been obvious to one of ordinary skill in the art. Bacteria with such multiple resistances are known in the art. See e.g. Morris et al., J. Infect. Diseases, 171:954-960; and Goble et al., N. Eng. J. Med., 328(8), 527-532. Thus, one of ordinary skill in the art would have been motivated to study, and test for drugs capable of treating infection by, bacteria with multiple antibiotic resistance.

Conclusion

19. No claims are allowed.

20. The following prior art references are made of record and are considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

Brosh et al., J. Bacter., 177(19): 5612-5621. This reference is deemed relevant to the patentability of the claimed inventions as it is considered redundant to the Aronshtam reference cited above. Brosh also teaches a dominant negative allele of a mismatch repair gene (identified as uvrDE221Q) that may be used in the described method of generating antibiotic resistant bacteria.

Karran et al., Cancer Surveys, 28 :69-85. This reference is not concerned with the mutation of bacterium in antibiotic resistant forms. However, the reference is relevant in that it teaches that cancer cells achieve resistance to anti-cancer therapeutics due to reduced mismatch repair capacity in the cells. Thus, the reference indicates that mismatch repair deficient cells may be useful in other cell types for the generation of drug resistant phenotypes.

Wu et al., J. Bacter., 176(17): 5393-5400. This reference is deemed relevant to the patentability of the claimed inventions as it is considered redundant to the Aronshtam reference cited above. Wu also teaches dominant negative alleles of a mismatch repair gene that may be used in the described method of generating antibiotic resistant bacteria.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner
February 21, 2003

JAMES HOUSEL 2/23/03
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